ODAC Meeting
BLA 125547 – Necitumumab

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FDA Presentation
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Outline

- Background
- Efficacy:
  - SQUIRE (pivotal study)
  - INSPIRE
- Safety:
  - Deaths
  - Anti-EGFR* class drugs adverse events
  - Thromboembolic events
- Summary
- Issues for ODAC

** EGFR = Epidermal Growth Factor Receptor*

Necitumumab

- Anti-EGFR recombinant human IgG1 monoclonal antibody designed to block the ligand binding site of the human EGFR

- Proposed Indication in combination with gemcitabine and cisplatin for the 1st-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC)

Randomized Controlled Studies to Support Approval

EFFICACY and SAFETY

SQUIRE (I4X-IE-JFCC; IMCL CP11-0806):
Gemcitabine/Cisplatin +/- Necitumumab
Metastatic **squamous** NSCLC

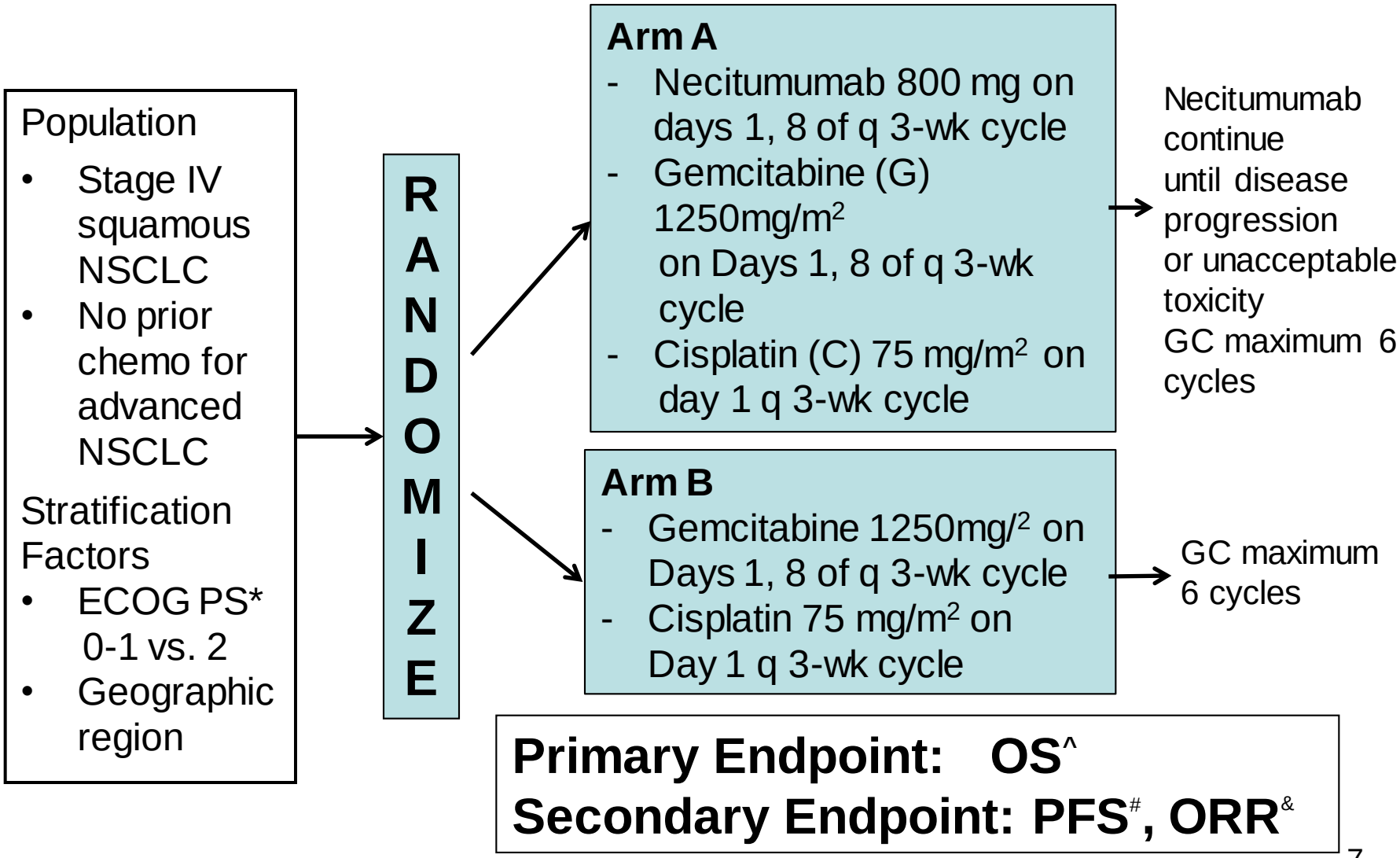
SAFETY

INSPIRE (I4X-IE-JFCB; IMCL CP11-0805):
Pemetrexed/Cisplatin +/- Necitumumab
Metastatic **non-squamous** NSCLC

SQUIRE STUDY

(I4X-IE-JFCC; IMCL CP11-0806)

SQUIRE Trial Design (Squamous NSCLC)



ECOG PS = Eastern Cooperative Oncology Group performance status; ^ OS = Overall Survival;
 # PFS = Progression-Free Survival; & ORR = Overall Response Rate

Statistical Analysis Plan

- Sample size: planned 1080
- Overall Survival (OS)
  - α=0.05 (2-sided)
  - 90% power for Hazard Ratio 0.80 (median from 11 to 13.75 months)
  - Number of death events needed = 844
- No interim analysis for OS
- Multiplicity adjustment for secondary endpoints: PFS and ORR
  - Hochberg approach

SQUIRE – Study Conduct

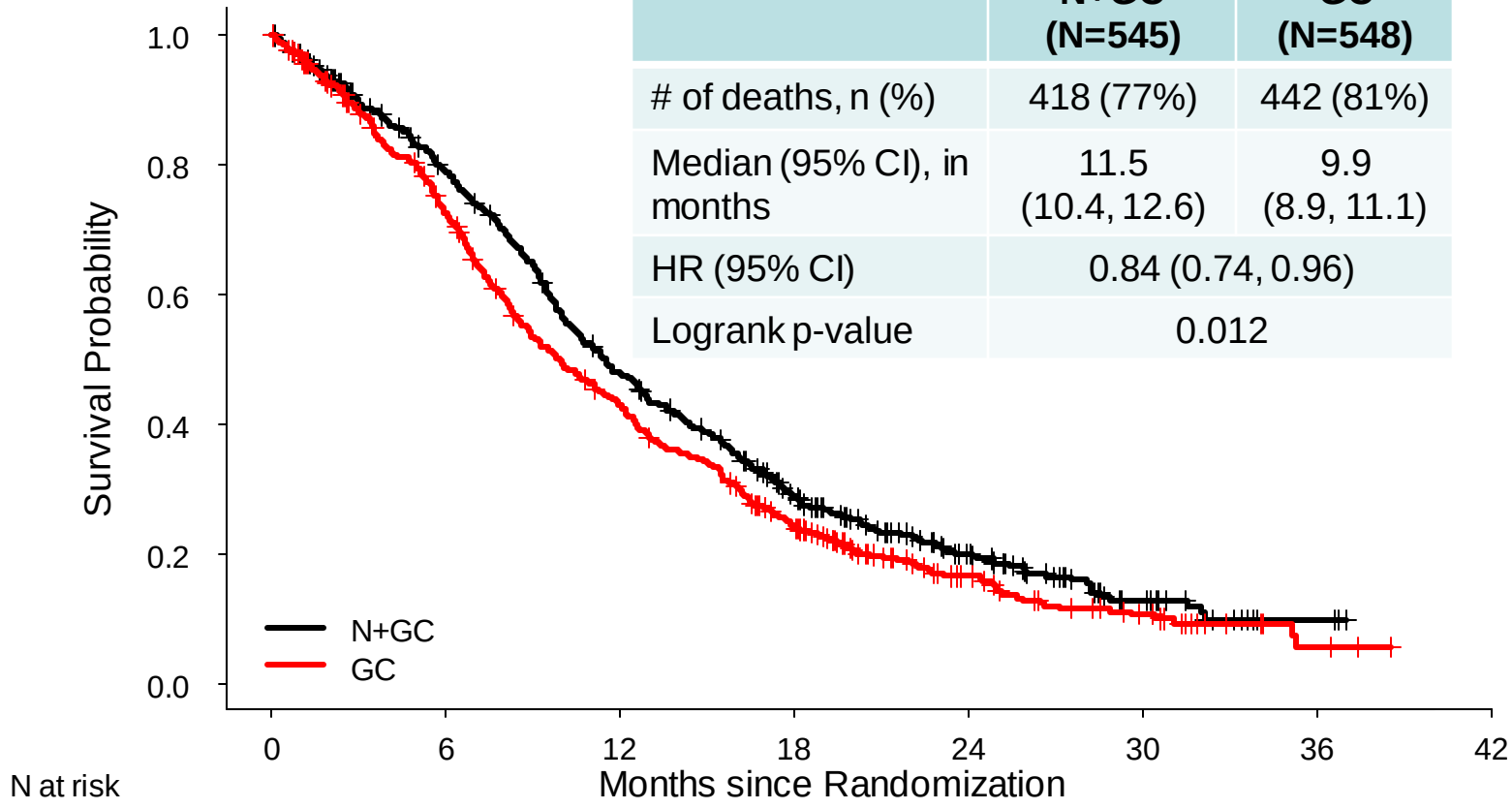
- N = 1093
- 2010 – 2012
- Worldwide: 26 countries in Europe, South America, Asia, North America, Australia
  - 36/1093 patients in U.S.
- Protocol violations:
  - Major violations: 0.9% vs. 0.9%
  - Significant violations: 8.6% vs. 5.1%

Demographics and Disease Characteristics

	Neci + GC (N=545)	GC (N=548)
Age median (range)	62 (32 – 84)	62 (32 - 86)
Gender: male	83%	84%
Race: White/Asian	84%/8%	83%/8%
ECOG PS 0/1	30%/61%	33/58
Smoker	92%	90%
Histology squamous	99.6%	99.6%
Prior therapy **Surgery** **Radiation Therapy** **Adj chemo**	 22% 8% 4%	 19% 8% 3%
Metastasis > 2 sites	55%	56%

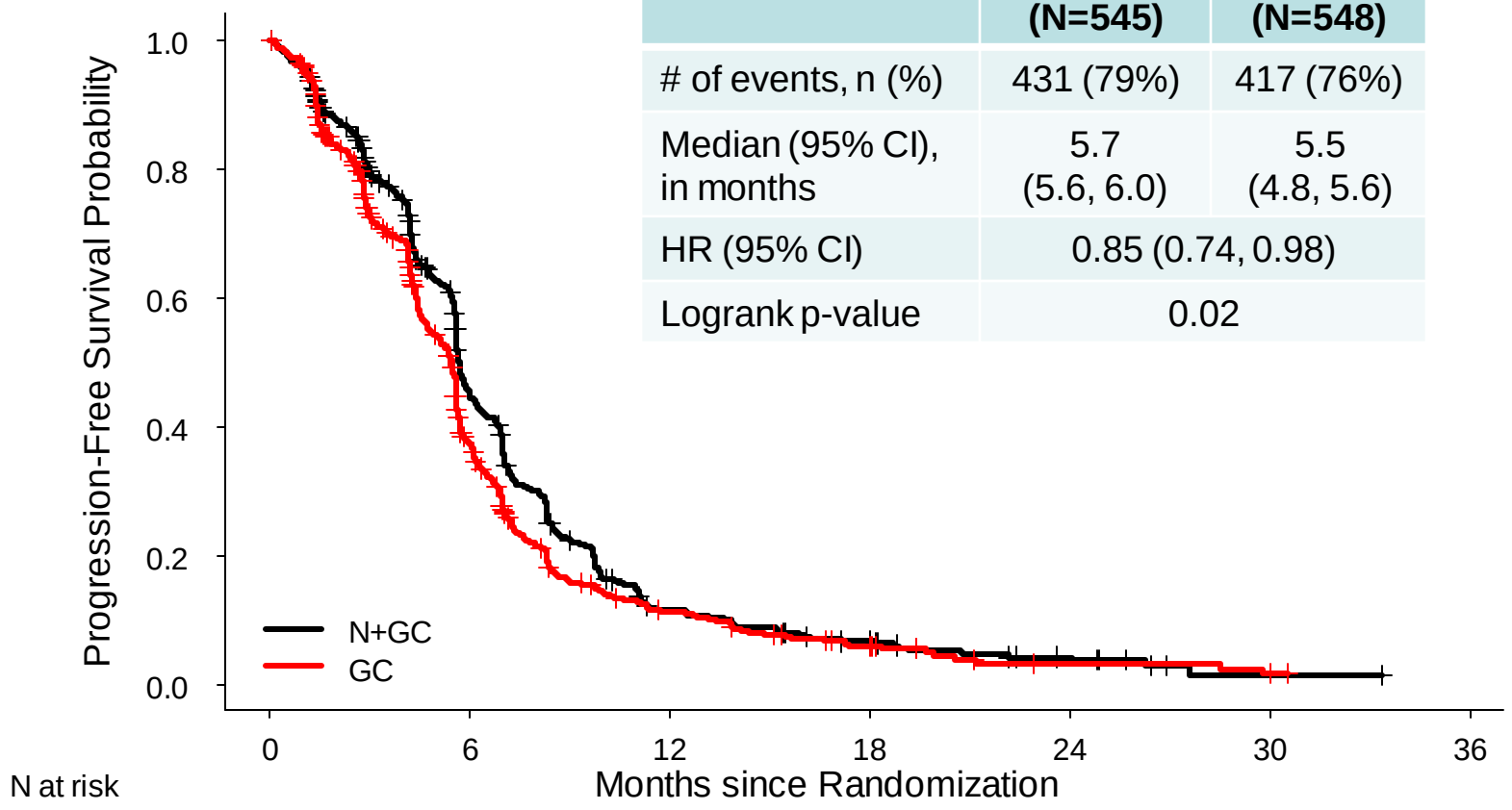
SQUIRE: Overall Survival

	N+GC (N=545)	GC (N=548)
# of deaths, n (%)	418 (77%)	442 (81%)
Median (95% CI), in months	11.5 (10.4, 12.6)	9.9 (8.9, 11.1)
HR (95% CI)	0.84 (0.74, 0.96)	
Logrank p-value	0.012	



SQUIRE: Progression-Free Survival

	N+GC (N=545)	GC (N=548)
# of events, n (%)	431 (79%)	417 (76%)
Median (95% CI), in months	5.7 (5.6, 6.0)	5.5 (4.8, 5.6)
HR (95% CI)	0.85 (0.74, 0.98)	
Logrank p-value	0.02	



Objective Response Rate

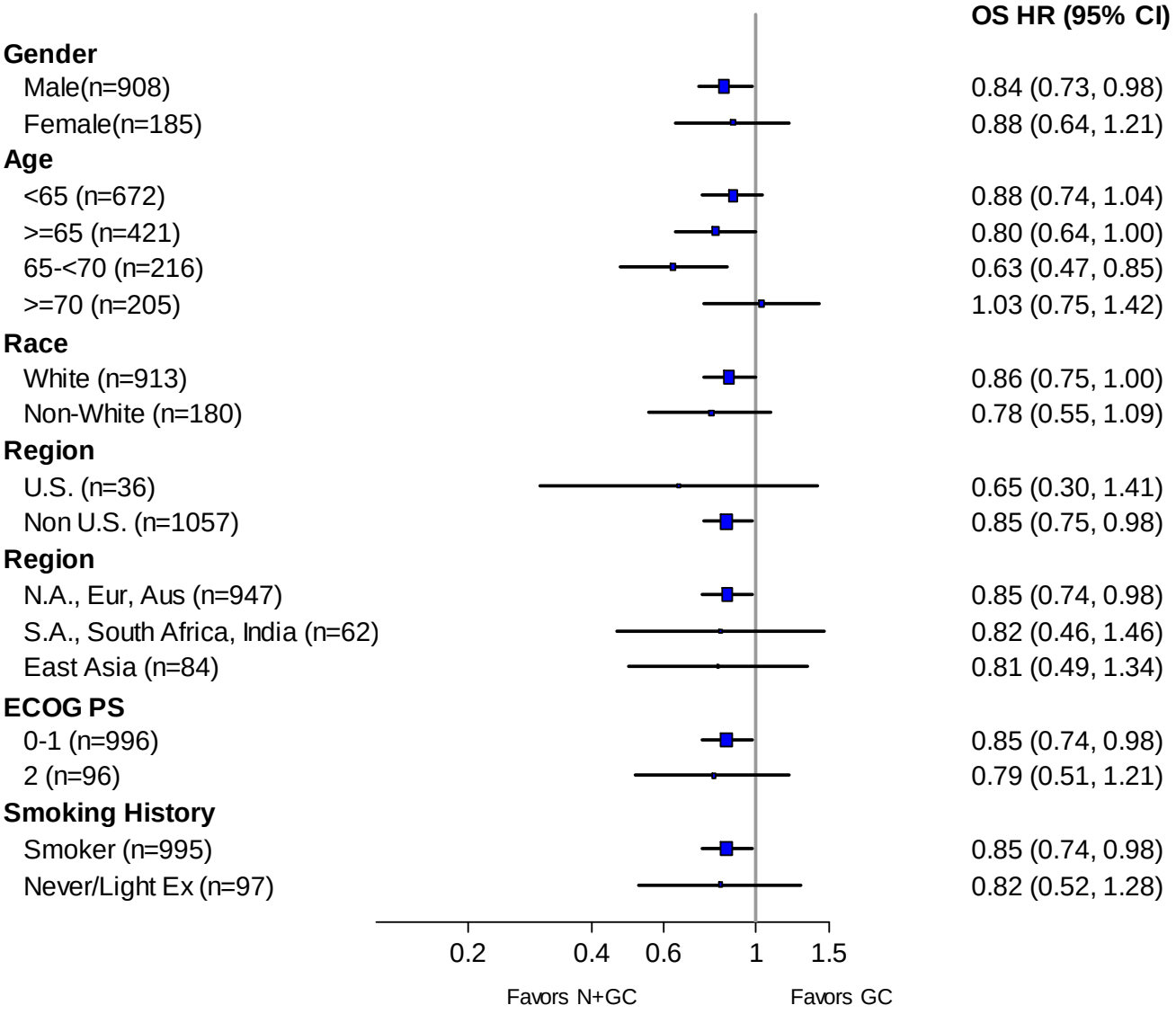
	GC+N (n=545)	GC (n=548)
ORR, n(%) Complete Response Partial Response	**170 (31%)** 0 170 (31%)	**158 (29%)** 3 (<1%) 155 (28%)
95% CI	**(27%, 35%)**	**(25%, 33%)**
p-value	**0.40**	
Median Duration of Response (months) **95% CI**	**5.6** **(5.1, 6.6)**	**4.9** **(4.3, 5.5)**

OS - Sensitivity Analyses

Sensitivity Analysis	N+GC Median	GC Median	HR (95% CI)
• ITT* population, un-stratified analysis	11.5	9.9	0.85 (0.74, 0.97)
• ITT population, per CRF[#] stratification data	11.5	9.9	0.83 (0.73,0.95)
• Per-protocol population (n=1072), stratified by IVRS^ data	11.5	9.9	0.85 (0.74, 0.97)
• Per-protocol population (N=1072), un-stratified analysis	11.5	9.9	0.86 (0.75, 0.98)
• Exactly 844 events as per protocol sample size calculation	11.5	9.9	0.83 (0.73, 0.95)
• Considering patients lost to FU[&] or withdrawing consent as events at 2 months after the date of last known alive	10.7	9.2	0.86 (0.75, 0.97)
• Censoring patients lost to FU or withdrawing consent at the study cutoff date	12.1	10.5	0.84 (0.74, 0.96)

**ITT = intent-to-treat; [#]CRF = case report form; ^ IVRS = Interactive Voice Response System; [&]FU = follow-up*

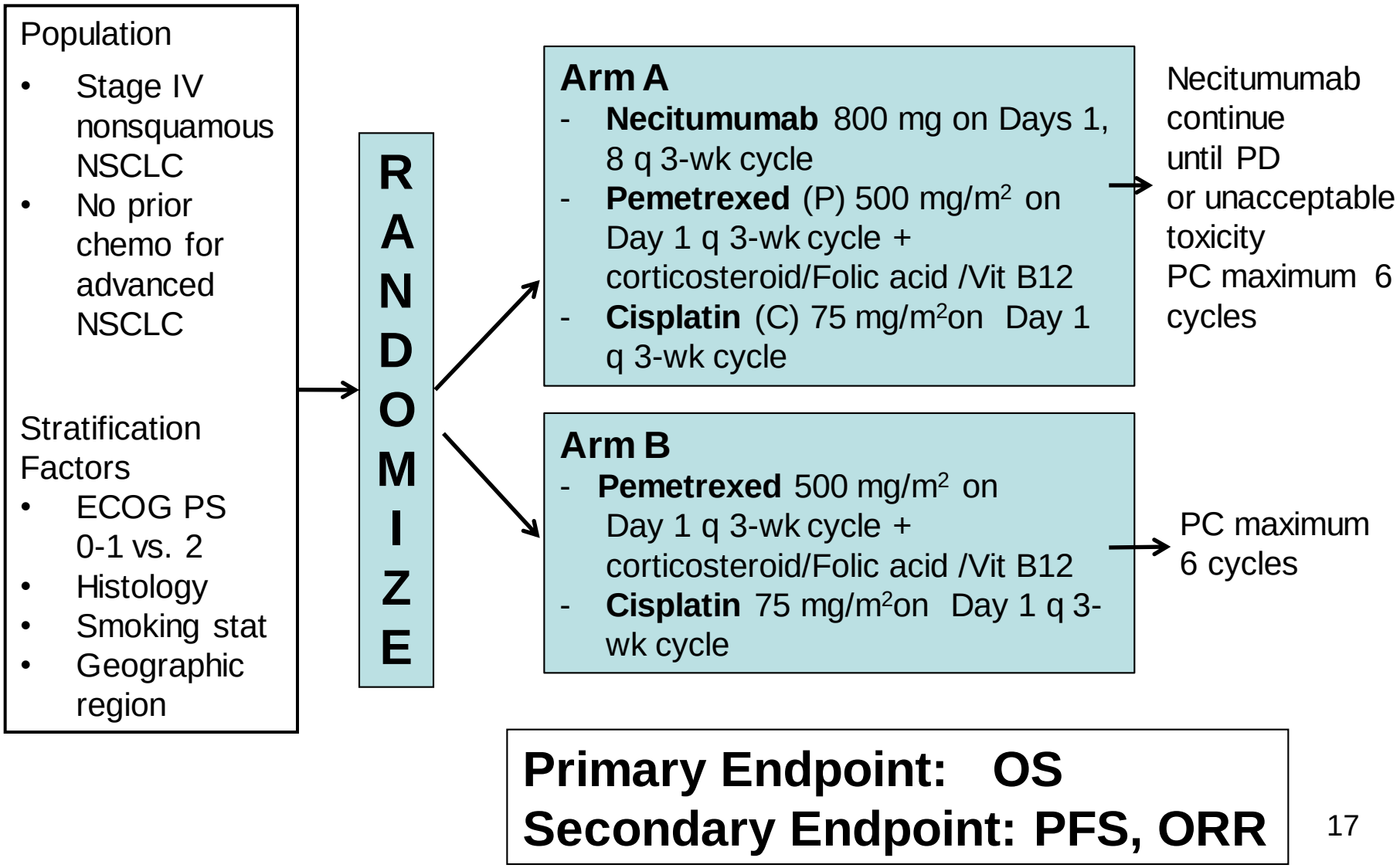
OS - Subgroup Analyses



INSPIRE STUDY

(I4X-IE-JFCB; IMCL CP11-0805)

INSPIRE Trial Design (Non-Squamous)



Primary Endpoint: OS
Secondary Endpoint: PFS, ORR

INSPIRE – Study Conduct

- Planned sample size: N=947 (enrolled: N= 633)
- Early closure by IDMC^ due to an ↑ in number of deaths attributed to thromboembolic events and other causes in the necitumumab arm compared to control
- Number of death events needed for the final OS analysis
  - originally planned: 723 deaths
  - final revised: 474 deaths
- Power reduced from 85% to 67.6% for a HR of 0.80 (11 vs. 13.75 months in median) at 0.05 two-sided significance level

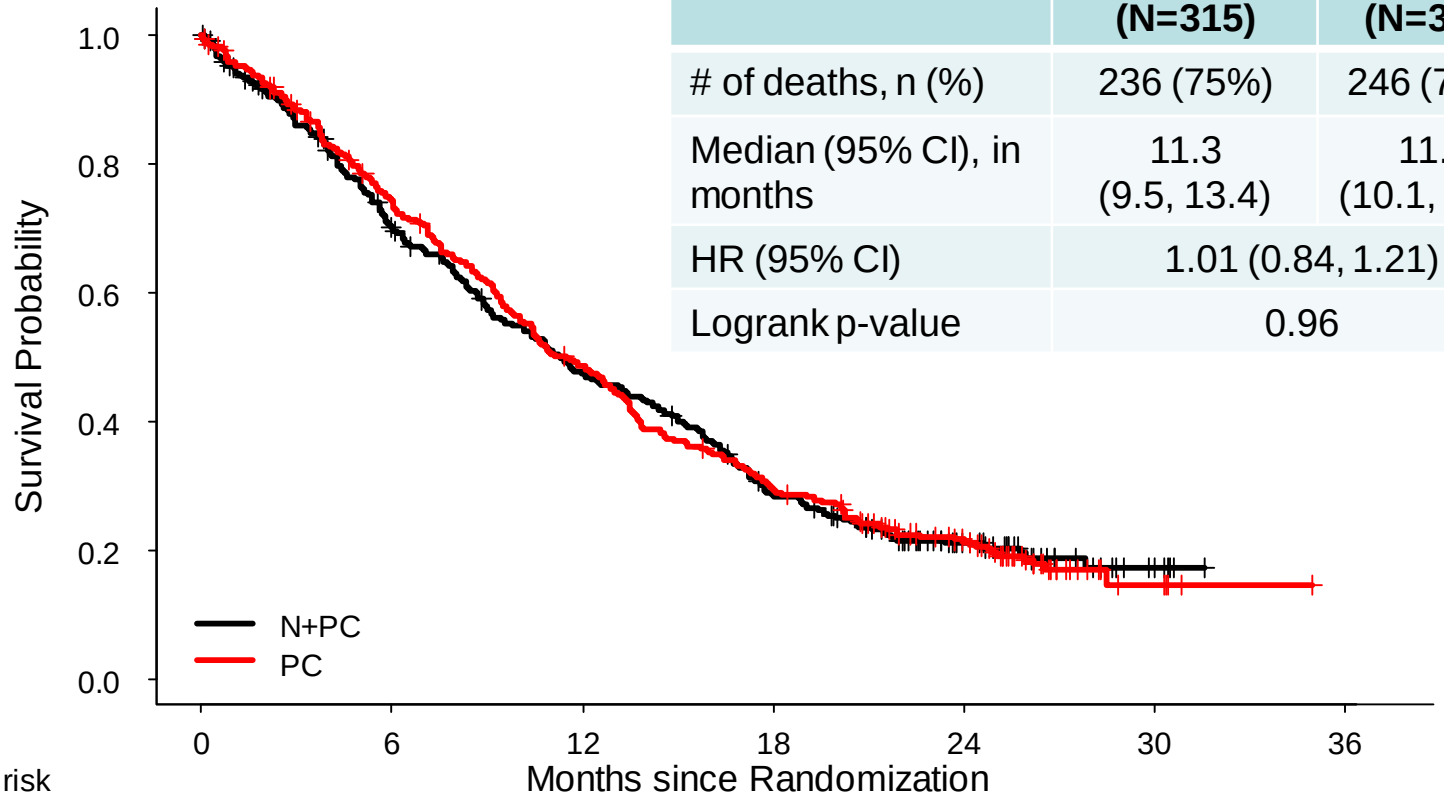
^IDMC = Independent Data Monitoring Committee

Demographics and Disease Characteristics

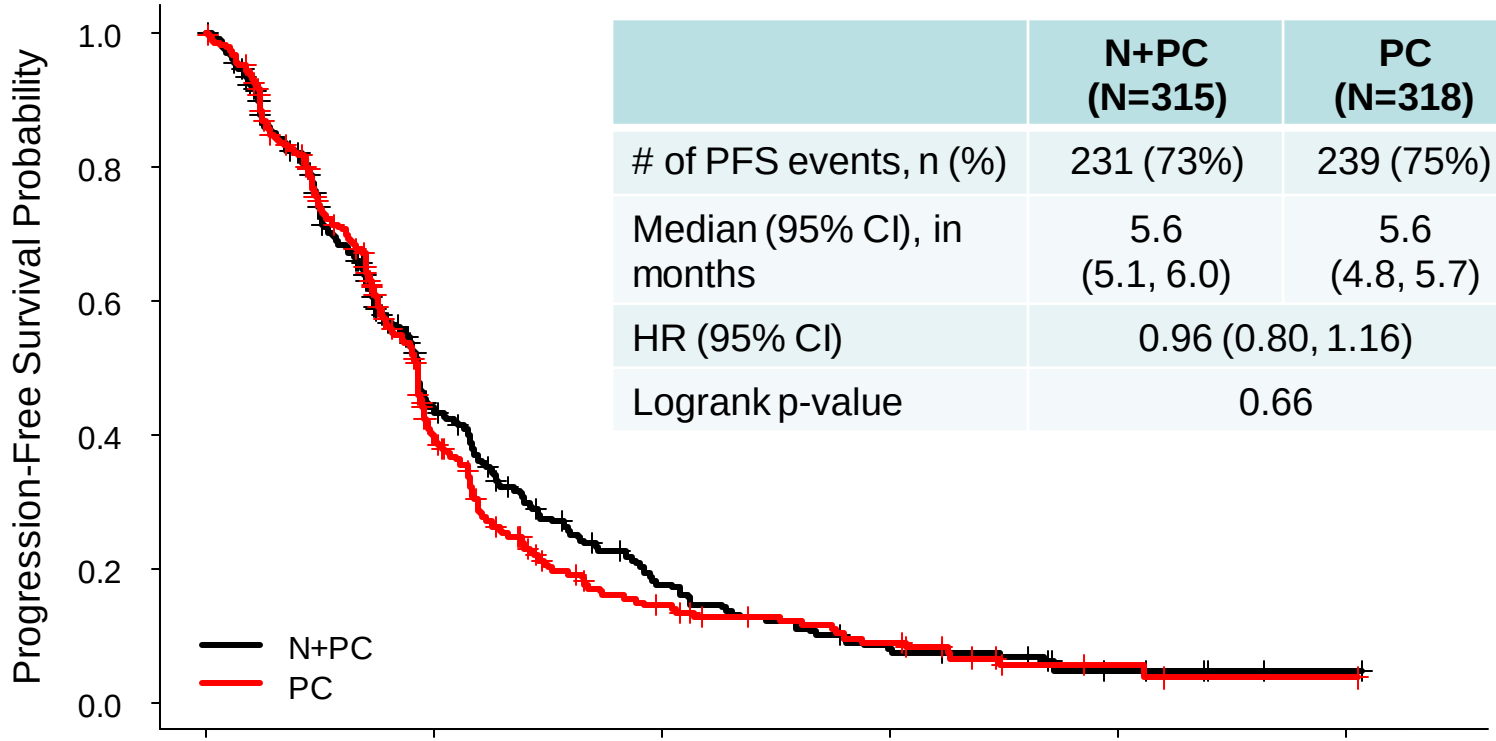
- **N =633 (315 N+PC arm, 318 PC arm)**
- Demographics and baseline characteristics similar across treatment arms
- Median age 61 years (range 26 - 88)
- 67% male, 94% ECOG PS 0 or 1
- 75% smoker
- Histology: 89% adenocarcinoma, 8% large cell

INSPIRE (Non-Squamous) - Overall Survival

	N+PC (N=315)	PC (N=318)
# of deaths, n (%)	236 (75%)	246 (77%)
Median (95% CI), in months	11.3 (9.5, 13.4)	11.5 (10.1, 13.1)
HR (95% CI)	1.01 (0.84, 1.21)	
Logrank p-value	0.96	



INSPIRE (Non-Squamous) - PFS



	N+PC (N=315)	PC (N=318)
# of PFS events, n (%)	231 (73%)	239 (75%)
Median (95% CI), in months	5.6 (5.1, 6.0)	5.6 (4.8, 5.7)
HR (95% CI)	0.96 (0.80, 1.16)	
Logrank p-value	0.66	

N at risk

N+PC	315	102	35	15	5	1
PC	318	98	27	14	3	1

Efficacy Summary

- **Squamous NSCLC (SQUIRE)**
  - 1.6 month median OS improvement (HR=0.84 logrank p=0.012)
  - 0.2 month median PFS improvement (HR=0.85, p=0.02).
  - No statistical improvement in ORR

- **Non-Squamous NSCLC (INSPIRE)**
  - No statistical improvement in OS, PFS or ORR

Safety

SQUIRE - Adverse Events

	Neci+ GC* % (N=538)	GC % (N=541)
Any Adverse Event	99%	98%
Any Serious	48%	38%
≥ Grade 3 Adverse Event	72%	62%
Deaths	77%	81%
Disease Progression	63%	68%
Adverse Event leading to Deaths	14%	13%
Death on treatment or ≤30 days	11%	11%

* Include AEs post chemotherapy (50% continued Necitumumab monotherapy)

SQUIRE - Death on Treatment or Within 30 Days of Last Dose (N ≥ 2)

MedDRA Preferred Term	Neci + GC * N=538 (%)	GC N=541 (%)
Due to an AE	**60 (11%)**	**57 (11%)**
NSCLC	18	18
Death NOS or sudden death	**10**	2
Hemoptysis or hemorrhage	5	**11**
Pneumonia or respiratory infection	6	5
Cardio-Respiratory or cardiac arrest	**5**	1
Myocardial infarction	2	0
Septic shock	0	2
Cardiac failure	0	2
Encephalopathy	0	2

Necitumumab + GC arm (N=538)
Sudden Death/Unknown < 30 Days Last Dose

(FDA's Attribution of cause of death)

	Age/Sex	Days on Study	Cause of death	Co-morbid conditions /Comment
1	61yo M	85	Sudden death	COPD, HTN, ECG abnl, **Gr 3 ↓ Mg++**
2	63yo M	111	Sudden Death	COPD, alcohol, **Gr 2 ↓ Mg++**
3	57yo M	245	Sudden Death	COPD, atherosclerosis
4	64yo M	21	Sudden Death	HTN, DM, COPD
5	55yo M	16	Sudden Death	CAD, MI
6	74yo M	9	Sudden death	COPD
7	63yo M	3	Sudden death	CAD, HTN, Hodgkin's
8	62yo M	81	Cardiac arrest	COPD, HTN, **Gr 3 ↓ Mg++**
9	62yo M	59	Unknown	CAD
10	54yo M	148	Unknown	No known risk
11	80yo M	90	Unknown	HTN, atrial fib., **Gr 2 ↓ Mg++**
12	61yo M	31	Unknown	COPD

GC arm (N=541)
Sudden death/unknown < 30 days last dose

ID	Age	Days	Cause of death	Comment
1	62yo M	74	Sudden death	-
2	46yo M	6	Sudden death	DM, meningitis
3	56yo M	3	Sudden death	Atrial fibrillation

Summary: Sudden deaths/unknown

Necitumumab + GC arm N = 12/538 2.2%
GC arm N = 3/541 0.5%

SQUIRE – Grade ≥ 3 AEs Occurring in ≥ 2% Patients

MedDRA Preferred Term	Neci + GC * % (N=538)	GC (N=541)
All AE grade ≥ 3	**72%**	**62%**
Neutropenia	24%	27%
Thrombocytopenia	10%	9%
Anemia	9%	9%
Hypomagnesemia	**9%**	**1%**
Leukopenia	**4%**	**6%**
Rash	**4%**	**<1%**
Asthenia	3%	3%
Pulmonary Embolism	**3%**	**1%**
Nausea	3%	3%
Vomiting	**3%**	**1%**
Fatigue	**2%**	**3%**

SQUIRE - Anti-EGFR Class Drugs Adverse Events

AE (composite terms)	Necitumumab + GC % (N=538)		GC % (N=541)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Skin Reactions - Rash	79% 76%	8% 7%	12% 10%	1% <1%
Hypomagnesemia AE Laboratory	 31% 81%	 9% 19%	 16% 70%	 1% 7%
Conjunctivitis	7%	<1%	2%	0
Diarrhea	16%	2%	11%	2%
Hypersensitivity/infusion reaction	2%	<1%	2%	0
Interstitial Lung Disease	1%	<1%	1%	1%

INSPIRE - Adverse Events

	Neci+ PC* % (N=304)	PC % (N=312)
≥ Grade 3 Adverse Event	72%	59%
Deaths	75%	78%
Disease Progression	61%	66%
AE leading to Deaths/other	15%	12%
Death on treatment or ≤30 days	14%	9%

INSPIRE - Death on Treatment or Within 30 Days of Last Dose (N ≥ 2)

(FDA's assessment of cause of death)

MedDRA PT	N + PC * % (N=304)	GC (N=312)
All	**43 (14%)**	**28 (9%)**
NSCLC	14	7
Respiratory Failure	5	3
Death NOS	**5**	**-**
Sudden death	**5**	**5**
Infection (sepsis, pneumonia, other)	7	4
Thromboembolic events	3	4
GI perforation	2	1

Summary: Sudden deaths/unknown
Necitumumab + PC arm N = 10/304 3.3%
PC arm N = 5/312 1.6%

Thromboembolic Events (TEs)

- Early safety signal in the INSPIRE study
- Study closed at the recommendation of IDMC due to ↑ of deaths of all causes and deaths possibly due to TEs in the necitumumab arm

INSPIRE - Thromboembolic Events

INSPIRE - Non-Squamous						
	Necitumumab +P/C N=304 (%)			P/C N=312 (%)		
	All	Gr≥3	Gr 5	All	Gr≥3	Gr 5
All TEs	17%	11%	2%	14%	6%	3%
Venous TE	13%	8%	1%	8%	4%	1%
Arterial TE	4%	3%	1%	6%	4%	2%

SQUIRE - Thromboembolic Events

SQUIRE - Squamous						
	Necitumumab +G/C N=538 (%)			G/C N=541 (%)		
	All	Gr≥3	Gr 5	All	Gr≥>3	Gr 5
All TEs	15%	9%	0.8%	9%	5%	0.4%
Venous TE	9%	5%	0.2 %	5%	3%	0.2%
Arterial TE	5%	4%	0.6 %	4%	2%	0.2%

SQUIRE - Venous TEs (N≥ 2)

	Necitumumab +G/C N=538		G/C N=541	
	All grades	Gr>3	All grades	Gr>3
MedDRA PT	49 (9%)	29 (5%)	29 (5%)	12 (2%)
Pulmonary Embolism	26 (5%)	20 (3.7%)	13 (2.4%)	10 (2%)
Deep Vein Thrombosis	10 (2%)	5 (1%)	5 (1%)	0
Thrombosis	4	1	3	0
Mesenteric vein thrombosis	2	1	1	2
Pulmonary arterial throm.	2	0	2	0
Pulmonary venous throm.	2	1	0	0
Limb vein throm/peripheral	2	1	0	0

Thromboembolic Events - Conclusion

- An increased incidence of venous TEs, some fatal, was observed with the addition of necitumumab to the platinum-doublet in both SQUIRE and INSPIRE studies.

- The incidence of venous TE was higher in the non-squamous (adenocarcinoma) population

SUMMARY

Efficacy

- **Squamous** NSCLC (SQUIRE) - Addition of necitumumab to gemcitabine/cisplatin:
  - OS: 1.6 month median improvement [HR=0.84 (95% CI 0.74; 0.96); logrank p=0.012]
  - PFS 0.2 month median improvement in PFS [HR=0.85 (95% CI 0.74, 0.98); logrank p=0.02)].
  - ORR: No statistically significant difference (31% vs. 29%).

- **Non-Squamous** NSCLC (INSPIRE) - No statistical improvement in OS, PFS or ORR with the addition of Necitumumab to pemetrexed/cisplatin

Safety

- Anti-EGFR related serious toxicities with the addition of necitumumab to gemcitabine/cisplatin: skin rash (8% vs.1%) and hypomagnesemia (9%vs.1%)

- Increased incidence of venous thromboembolic events (9% vs. 5% in SQUIRE, 13% vs. 8% in INSPIRE), some fatal.

- Increase incidence of sudden deaths/death NOS (2.2% vs. 0.5% in SQUIRE, 3.3% vs. 1.6% in INSPIRE)

Issues of the Advisory Committee

For discussion:

•Please discuss whether the INSPIRE trial results in the **non-squamous** NSCLC population impact the benefit: risk assessment of necitumumab for **squamous** NSCLC.

•Please discuss whether the efficacy and safety results of SQUIRE in **squamous** cell NSCLC support a positive benefit: risk assessment of necitumumab in combination with gemcitabine/cisplatin in the proposed population.

Backup Slides Shown

Necitumumab + GC						
ID	Age	Day of therapy/ day since last study drug	Primary Cause of Death	Comments	Risk factors	Reviewer's Comment
	61m	85 d, 13d 10/14/10 – 12/29/10 C4 D8	Unknown (Sudden Death)	Found dead at home 1/10/11 Mg++: (0.7 – 1.1 mmol) 0.77 (10/14/10) 0.61 mmol/L (11/16/10) 0.4 mmol/L (12/8/10) 0.37 mmol/L (12/21/10), **0.34 mmol (12/29/10),** K and Ca normal on 12/29/10	HTN, COPD, ECG abnormal (LPHB), Other AEs: Gr 3 Syncope (12/8/10), Gr 3 diarrhea, dehydration 12/13-12/15)	+ Risk factors for sudden death. Progressive worsening of hypomagnesemia (from normal baseline to grade 3 C4D8) 6 weeks prior to death, apparently untreated. Electrolytes on the day of death (1/10/11) not known. Untreated hypomagnesemia and other electrolyte inbalance most likely contributed to death

	62w m	81/18 1/11/12 – 3/14/12 C3 d 8	Cardiac arrest	Died at home, after feeling weak and fatigued cause of death cardiac arrest 3/31/2012 **3/20/12 –** **Mg 0.39 (grade 3)** **K 3.1** **Ca 1.97** **Action taken –none (True ?) –** **CSR page 436/2759 – see below**	COPD, HTN (bisoprolol, fluticasone, salmeterol, aminophylline, tramadol)	Investigator assessed cause of death as disease progression Reviewer's disagree – Pre-existing risk-factors. Severe electrolyte imbalance (untreated?) most likely contributed to death.